

What is claimed:

1. A method for identifying an insulin response modulator, comprising contacting a composition comprising IRAP or a bioactive fragment thereof and TAP or a bioactive fragment thereof with a test compound and determining the ability of the test compound to modulate binding of the IRAP or bioactive fragment to the TAP or bioactive fragment, such that an insulin response modulator is identified.
2. A method for identifying an insulin response modulator, comprising contacting a donor vesicle fraction comprising GLUT4 vesicles with a test compound and determining the ability of the test compound to modulate GLUT4 vesicle translocation, such that an insulin response modulator is identified, wherein said donor fraction is associated with TAP or a bioactive fragment thereof prior to contacting with said test compound.
3. The method of claim 2, wherein determining the ability of the test compound to modulate GLUT4 vesicle translocation comprises detecting translocation of a GLUT4 vesicle component to an acceptor vesicle fraction.
4. The method of claim 3, wherein determining the ability of the test compound to modulate GLUT4 vesicle translocation comprises detecting a change in GLUT4 levels in said acceptor fraction.
5. The method of claim 4, wherein detecting a change in GLUT4 levels in said acceptor fraction comprises detecting GLUT4 levels in said acceptor fraction after contacting said donor fraction with the test compound as compared to a control acceptor fraction.
6. The method of claim 3, wherein determining the ability of the test compound to modulate GLUT4 vesicle translocation comprises detecting a change in IRAP levels in said acceptor fraction.
7. The method of claim 6, wherein detecting a change in IRAP levels in said acceptor fraction comprises detecting IRAP levels in said acceptor fraction after contacting said donor fraction with the test compound as compared to a control acceptor fraction.

8. The method of any one of claims 2-7, wherein said donor fraction is a GLUT4 vesicle preparation or a low density microsomal fraction.

9. The method of any one of claims 3-7, wherein said acceptor fraction is a plasma membrane fraction.

10. The method of any one of claims 3-7, wherein said acceptor fraction is a plasma membrane fraction and said donor fraction is a GLUT4 vesicle preparation or a low density microsomal fraction.

11. A method for identifying an insulin response modulator, comprising contacting a cell that expresses TAP or a bioactive fragment thereof with a test compound and determining the ability of the test compound to modulate an activity selected from the group consisting of glucose uptake, GLUT4 vesicle translocation, IRAP translocation and extracellular aminopeptidase activity, such that an insulin response modulator is identified.

12. The method of claim 11, wherein said cell overexpresses TAP.

13. The method of claim 11, wherein said cell overexpresses IRAP.

14. The method of claim 11, wherein the ability of the test compound to modulate GLUT4 vesicle translocation or IRAP translocation is determined.

15. The method of any one of claims 3-7, wherein determining the ability of the test compound to modulate GLUT4 vesicle translocation comprises detecting fluorescence resonance energy transfer from a component of the donor fraction to a component of the acceptor fraction.

16. A method for identifying an insulin response modulator, comprising contacting an assay vesicle with a test compound, wherein said assay vesicle is associated with TAP or a bioactive fragment thereof prior to contacting with said test compound, and determining the ability of the test compound to modulate release of the assay vesicle from the TAP or bioactive fragment thereof, such that an insulin response modulator is identified.

17. The method of claim 16, wherein the TAP or bioactive fragment thereof is immobilized.

18. The method of claim 16, wherein the TAP or bioactive fragment thereof  
5 is bound to a membrane.

19. The method of claim 16, wherein the TAP or bioactive fragment thereof is immobilized to a suitable assay vessel.

20. The method of claim 16, wherein the assay vesicle is detectably labeled.  
10

21. The method of claim 16, wherein the assay vesicle is radioactively labeled.

22. The method of claim 16, wherein determining the ability of the test  
15 compound to modulate assay vesicle release, comprises comparing the amount of radioactive label in association with the immobilized TAP or bioactive fragment thereof with an appropriate control.

23. The method of claim 16, wherein the assay vesicle comprises a  
20 fluorescent dye.

24. The method of claim 23, wherein determining the ability of the test  
25 compound to modulate assay vesicle release, comprises comparing the amount of fluorescent label in association with the immobilized TAP or bioactive fragment thereof with an appropriate control.

25. The method of claim 16, wherein the assay vesicle is immobilized.

26. The method of claim 25, wherein the assay vesicle is bound to a  
30 membrane.

27. The method of claim 25, wherein the assay vesicle is immobilized to a  
suitable assay vessel.

28. The method of claim 25, wherein the TAP or bioactive fragment thereof  
35 is detectably labeled.

29. The method of claim 25, wherein the TAP or bioactive fragment thereof is radioactively labeled.

5 30. The method of claim 25, wherein the TAP or bioactive fragment thereof is fluorescently labeled.

31. The method of any one of the preceding claims, wherein the modulator identified is a positive modulator.  
10

32. A modulator identified by any one of the preceding claims.

33. A method for the identification of a potential insulin response modulator comprising contacting a cytosolic fraction comprising TAP or a bioactive fragment thereof with a test compound and determining the phosphorylation state of the TAP or bioactive fragment in the presence of the test compound as compared to an appropriate control, wherein the test compound is a potential insulin response modulator based on the ability to effect the phosphorylation state of TAP or a bioactive fragment thereof.  
15

20 34. A method for identifying an IRAP:TAP modulator, comprising contacting a composition comprising IRAP or bioactive fragment thereof and TAP or bioactive fragment thereof with a test compound and determining the ability of the test compound to enhance binding of the IRAP or bioactive fragment thereof to the TAP or bioactive fragment thereof, such that the modulator is identified.  
25

35. A method for identifying an IRAP:TAP modulator, comprising contacting a composition comprising IRAP or bioactive fragment thereof and TAP or bioactive fragment thereof with a test compound and determining the ability of the test compound to inhibit binding of the IRAP or bioactive fragment thereof to the TAP or bioactive fragment thereof, such that the modulator is identified.  
30

36. A method of modulating GLUT4 translocation in a subject comprising administering to said subject an insulin response modulator identified according to the methods of any one of claims 1-31, 34 or 35, such that GLUT4 translocation is modulated.  
35

37. A method of enhancing glucose clearance in an insulin resistant subject, comprising administering to said subject an insulin response modulator identified according to claim 31, such that glucose clearing in said subject is enhanced.

5           38. A method of regulating blood glucose levels in a subject comprising administering to said subject an insulin response modulator identified according to the methods of any one of claims 1-31, 34 or 35, such that blood glucose levels are regulated.

10           39. An antibody that specifically binds to an IRAP-interacting domain of TAP, said antibody being capable of interfering with the IRAP:TAP interaction.

40. A pharmaceutical composition comprising the antibody of claim 39.

15           41. An antibody that specifically binds to TAP, said antibody being specific for the antigenic determinant from amino acids 40-57 or amino acids 888-905 of human TAP.

42. A pharmaceutical composition comprising the modulator of claim 32.

20

43. A pharmaceutical composition comprising an IRAP-interacting domain of TAP, said IRAP-interacting domain being capable of interfering with the IRAP:TAP interaction.

25           44. A method for identifying a compound suitable for use in treating diabetes or insulin resistance in a subject, said method comprising contacting a cell capable of expressing TAP mRNA with a test compound and determining the effect of the test compound on expression of TAP mRNA, wherein a stimulatory effect is indicative of the compound being suitable for use in treating diabetes or insulin resistance in said  
30 subject.

45. A method for identifying a compound suitable for use in treating diabetes or insulin resistance in a subject, said method comprising contacting a cell capable of expressing TAP protein with a test compound and determining the effect of the test  
35 compound on expression of TAP protein, wherein a stimulatory effect is indicative of the compound being suitable for use in treating diabetes or insulin resistance in said subject.

46. A method for identifying a compound suitable for use in treating diabetes or insulin resistance in a subject, said method comprising contacting a cell which expresses TAP protein with a test compound and determining the effect of the test compound on a biological activity of the TAP protein, wherein a stimulatory effect is indicative of the compound being suitable for use in treating diabetes or insulin resistance in said subject.

47. A method for identifying a compound suitable for use in treating diabetes or insulin resistance in a subject, said method comprising contacting a TAP protein or biologically active portion thereof with a test compound and determining the effect of the test compound on a biological activity of the TAP protein or portion, wherein a stimulatory effect is indicative of the compound being suitable for use in treating diabetes or insulin resistance in said subject.

48. A compound identified by the method of any one of claims 44-47.

49. The compound of claim 48 formulated with a pharmaceutically-acceptable carrier.

50. A method of increasing expression of TAP in a subject comprising administering to the subject a compound identified by the method of any one of claims 44-47, such that TAP expression is increased.

51. The method of claim 50, wherein TAP mRNA levels are increased

52. The method of claim 50, wherein TAP protein levels are increased.

53. A method of treating diabetes in a subject comprising administering to the subject a compound identified by the method of any one of claims 44-47.

54. A method of treating diabetes in a subject comprising administering to the subject a compound that increases the expression of TAP in said subject, such that diabetes is treated.

55. The method of claim 54, wherein compound is selected from the group consisting of a TAP nucleic acid molecule, a plasmid comprising a TAP nucleic acid

molecule, TAP adenovirus, a TAP retrovirus, a TAP protein or biologically active portion thereof, an antibody or biologically active portion thereof, a peptide, a peptidomimetic, a non-peptide oligomer and a small molecule.

5           56.     The method of any one of claims 53-55, wherein the subject is suffering from type II diabetes.

              57.     A method of treating insulin resistance in a subject comprising administering to the subject a compound identified by the method of any one of claims  
10   44-57, such that insulin resistance is treated.

              58.     A method of treating insulin resistance in a subject comprising administering to the subject a compound that increases the expression of TAP in said subject, such that insulin resistance is treated.

15           59.     The method of claim 58, wherein compound is selected from the group consisting of a TAP nucleic acid molecule, a plasmid comprising a TAP nucleic acid molecule, TAP adenovirus and a TAP retrovirus.

20           60.     The method of claim 58, wherein compound is selected from the group consisting of a TAP protein or biologically active portion thereof, an antibody or biologically active portion thereof, a peptide, a peptidomimetic, a non-peptide oligomer and a small molecule.

25           61.     A method of increasing TAP expression or activity in a cell comprising contacting said cell with a compound identified by the method of any one of claims 44-47, such that TAP expression or activity in said cell is increased.

              62.     A method of increasing TAP expression or activity in a cell comprising  
30   contacting said cell with a compound that increases the expression of TAP in said cell, such that TAP expression or activity in said cell is increased.

              63.     The method of claim 62, wherein compound is selected from the group consisting of a TAP nucleic acid molecule, a plasmid comprising a TAP nucleic acid  
35   molecule, TAP adenovirus and a TAP retrovirus.

64. The method of claim 62, wherein compound is selected from the group consisting of a TAP protein or biologically active portion thereof, an antibody or biologically active portion thereof, a peptide, a peptidomimetic, a non-peptide oligomer and a small molecule.

5

65. A pharmaceutical composition comprising a cell, said cell overexpressing a TAP protein or biologically active portion thereof, and a pharmaceutically-acceptable carrier.

10

66. The method of any one of claims 61-64, wherein the cell is a muscle cell or a precursor thereof.

67. The method of any one of claims 61-64, wherein the cell is an adipocyte or a precursor thereof.

15

68. A method of treating a subject having diabetes or an insulin-resistant subject comprising obtaining cells from said subject, treating said cells with a compound identified by the method of any one of claims 44-47, and administering said treated cells to said subject such that diabetes or insulin-resistance in said subject is treated.

20

69. A method of treating a subject having diabetes or an insulin-resistant subject comprising obtaining cells from said subject, treating said cells with a compound that increases expression of TAP in said cell, and administering said treated cells to said subject such that diabetes or insulin-resistance in said subject is treated.

25

70. The method of claim 69, wherein compound is selected from the group consisting of a TAP nucleic acid molecule, a plasmid comprising a TAP nucleic acid molecule, TAP adenovirus and a TAP retrovirus.

30

71. The method of claim 69, wherein compound is selected from the group consisting of a TAP protein or biologically active portion thereof, an antibody or biologically active portion thereof, a peptide, a peptidomimetic, a non-peptide oligomer and a small molecule.